



ARX gene

aristaless related homeobox

Normal Function

The *ARX* gene provides instructions for producing a protein that regulates the activity of other genes. On the basis of this action, the ARX protein is called a transcription factor. The *ARX* gene is part of a larger family of homeobox genes, which act during early embryonic development to control the formation of many body structures. Specifically, the ARX protein is believed to be involved in the development of the brain, pancreas, testes, and muscles used for movement (skeletal muscles).

In the pancreas, testes, and skeletal muscles, the ARX protein helps to regulate the process by which cells mature to carry out specific functions (differentiation). Within the developing brain, the ARX protein is involved with movement (migration) and communication of nerve cells (neurons). In particular, this protein regulates genes that play a role in the migration of specialized neurons (interneurons) to their proper location. Interneurons relay signals between other neurons.

Health Conditions Related to Genetic Changes

Early infantile epileptic encephalopathy 1

Mutations in the *ARX* gene can cause early infantile epileptic encephalopathy 1 (EIEE1), a disorder characterized by recurrent seizures called infantile spasms that begin in the first year of life. Children with this condition also have intellectual disability.

The normal ARX protein contains four regions where a protein building block (amino acid) called alanine is repeated multiple times. These stretches of alanines are known as polyalanine tracts. The most common *ARX* gene mutations that cause EIEE1 add extra alanines to the first or second polyalanine tract in the ARX protein. This type of mutation is called a polyalanine repeat expansion. Research suggests that these polyalanine repeat expansions reduce the amount of ARX protein in cells, although the mechanism is unclear. Other *ARX* gene mutations that cause this condition are believed to reduce the function of the ARX protein. A shortage of ARX function is thought to impair the normal development and migration of certain interneurons, which likely underlies infantile spasms and other neurological problems characteristic of EIEE1.

Partington syndrome

A few mutations in the *ARX* gene have been identified in people with Partington syndrome, a neurological disorder that causes intellectual disability and a group of

movement problems called focal dystonia that primarily affects the hands. The most common mutation that causes Partington syndrome, a duplication of genetic material written as c.428_451dup, adds extra alanines to the second polyalanine tract in the ARX protein. The polyalanine repeat expansion likely reduces the amount of ARX protein or impairs its function and may disrupt normal interneuron migration in the developing brain, leading to the intellectual disability and dystonia characteristic of Partington syndrome.

X-linked lissencephaly with abnormal genitalia

At least 30 mutations in the *ARX* gene can cause X-linked lissencephaly with abnormal genitalia (XLAG). This condition is characterized by abnormal brain development that results in the brain having a smooth appearance (lissencephaly) instead of its normal folds and grooves. Males with XLAG also have abnormal genitalia. The *ARX* gene mutations that cause XLAG lead to the production of a nonfunctional ARX protein or to a complete absence of ARX protein. As a result, the ARX protein cannot perform its role regulating the activity of genes important for interneuron migration. In addition to impairing normal brain development, a lack of functional ARX protein disrupts cell differentiation in the testes, leading to the development of abnormal genitalia. It is thought that the disruption of ARX protein function in the pancreas plays a role in digestive issues, including chronic diarrhea, experienced by individuals with XLAG.

Females with an *ARX* gene mutation typically have less severe signs and symptoms than males. Affected females may have an absence of the tissue connecting the left and right halves of the brain (agenesis of the corpus callosum), some degree of intellectual disability, and recurrent seizures (epilepsy). Some females with an *ARX* gene mutation experience no symptoms.

Other disorders

Mutations in the *ARX* gene can cause a variety of conditions that impair brain function. Some *ARX* gene mutations result in intellectual disability without other neurological problems. Because the *ARX* gene is on the X chromosome, this condition is known as X-linked intellectual disability (XLID) or sometimes nonsyndromic XLID. XLID can occur in combination with other neurological problems as part of distinct conditions called XLID syndromes. *ARX* gene mutations account for 9.5 percent of all cases of XLID.

ARX gene mutations cause several XLID syndromes, including X-linked lissencephaly with abnormal genitalia, early infantile epileptic encephalopathy 1, and Partington syndrome (described above). Another is X-linked myoclonic epilepsy with intellectual disability and spasticity, which causes intellectual disability and epilepsy. *ARX* gene mutations also cause several syndromes that include structural brain malformations. These include Proud syndrome, which is characterized by agenesis of the corpus callosum as well as abnormal male genitalia, and hydranencephaly with

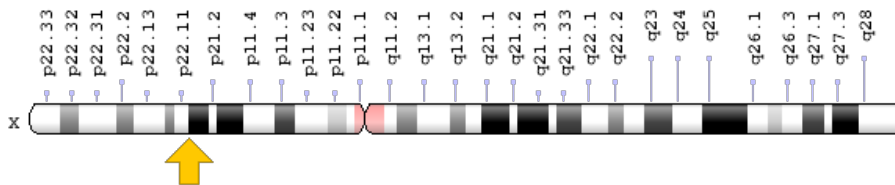
abnormal genitalia, which results in a fluid-filled sac replacing most of the brain tissue (hydranencephaly) and abnormal male genitalia.

For unknown reasons, the same mutation can result in the development of different conditions in different people, even among individuals within the same family. It is not clear why mutations in the *ARX* gene cause this array of conditions; researchers suggest that other genetic and environmental factors that have not been identified are likely involved.

Chromosomal Location

Cytogenetic Location: Xp21.3, which is the short (p) arm of the X chromosome at position 21.3

Molecular Location: base pairs 25,003,694 to 25,015,948 on the X chromosome (Homo sapiens Annotation Release 109, GRCh38.p12) (NCBI)



Credit: Genome Decoration Page/NCBI

Other Names for This Gene

- aristaless-related homeobox, X-linked
- ARX_HUMAN
- ISSX
- MRX29
- MRX32
- MRX33
- MRX36
- MRX38
- MRX43
- MRX54
- MRXS1
- PRTS

Additional Information & Resources

Educational Resources

- Neuroscience (second edition, 2001): Early Brain Development
<https://www.ncbi.nlm.nih.gov/books/NBK11113/>
- Neuroscience (second edition, 2001): Neuronal Migration
<https://www.ncbi.nlm.nih.gov/books/NBK10831/>

Scientific Articles on PubMed

- PubMed
<https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28ARX%5BTIAB%5D%29+OR+%28aristales+related+homeobox%5BTIAB%5D%29%29+AND+%28%28Genes%5BMH%5D%29+OR+%28Genetic+Phenomena%5BMH%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D>

Catalog of Genes and Diseases from OMIM

- ARISTALESS-RELATED HOMEBOX, X-LINKED
<http://omim.org/entry/300382>
- CORPUS CALLOSUM, AGENESIS OF, WITH ABNORMAL GENITALIA
<http://omim.org/entry/300004>
- EPILEPTIC ENCEPHALOPATHY, EARLY INFANTILE, 1
<http://omim.org/entry/308350>
- MENTAL RETARDATION, X-LINKED, WITH OR WITHOUT SEIZURES, ARX-RELATED
<http://omim.org/entry/300419>

Research Resources

- Atlas of Genetics and Cytogenetics in Oncology and Haematology
http://atlasgeneticsoncology.org/Genes/GC_ARX.html
- ClinVar
<https://www.ncbi.nlm.nih.gov/clinvar?term=ARX%5Bgene%5D>
- HGNC Gene Symbol Report
https://www.genenames.org/data/gene-symbol-report#!/hgnc_id/HGNC:18060
- Monarch Initiative
<https://monarchinitiative.org/gene/NCBIGene:170302>
- NCBI Gene
<https://www.ncbi.nlm.nih.gov/gene/170302>
- UniProt
<https://www.uniprot.org/uniprot/Q96QS3>

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